Texas Medicaid/CHIP Vendor Drug Program
Drug Utilization Criteria For Outpatient Use Guidelines
Serotonin 5-HT$_{1B/1D}$ Receptor Agonists

About
Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Publication History
Revised December 2016; December 2014; March 2013; April 2011; October 2008; May 2007; December 2006; August 2003; July 2002; November 2001; September 2001; August 2000; October 1999. Developed August 1998.

---

1. Dosage [*]

Adults
Serotonin 5-HT$_{1B/1D}$ receptor agonists (SRAs) are FDA-approved to manage acute migraine headache attacks with or without aura. Injectable sumatriptan is also FDA-approved to manage cluster headache episodes. The maximum recommended adult doses for available SRAs are summarized in Table 1. Dosages exceeding these recommendations will be reviewed.

Table 1: Maximum Recommended Daily Adult Dosages for SRAs[1-17]

Drug	Dosage Form/Strength	Maximum Daily Dosage
Monotherapy		
almotriptan (Axert®, **generic**)	tablets (6.25 mg, 12.5 mg)	25 mg/day
eletriptan (Relpax®)	tablets (20 mg, 40 mg)	80 mg/day
frovatriptan (Frova®, **generic**)	tablets (2.5 mg)	7.5 mg/day
naratriptan (Amerge®, generic)	tablets (1 mg, 2.5 mg)	5 mg/day
rizatriptan Maxalt®, generic	tablets (5 mg, 10 mg)	30 mg/day
Maxalt -MLT®, generic	orally-disintegrating tablets (5 mg, 10 mg)	30 mg/day
propranolol patients		*15 mg/day*
sumatriptan Imitrex®, generic	intranasal spray (5 mg/spray, 20 mg/spray - 6 per package)	40 mg/day
Onzetra Xsail®	**intranasal powder (11 mg/actuation)**	**44 mg/day***
Imitrex®, generic	oral tablets (25 mg, 50 mg, 100 mg)	200 mg/day
Imitrex®, generic **Sumavel® DosePro®** **Zembrace™ SymTouch™**	subcutaneous injection (4 mg and 6 mg STATdose system, 6 mg/0.5 mL single dose vial) **4 mg and 6 mg needle-free delivery system** **3 mg/0.5 mL autoinjector**	12 mg/day

Table 1: Maximum Recommended Daily Adult Dosages for SRAs (continued)[1-17]		
Drug	**Dosage Form/Strength**	**Maximum Daily Dosage**
zolmitriptan Zomig®, generic	tablets (2.5 mg, 5 mg)	10 mg/day
Zomig-ZMT®, generic	orally disintegrating tablets (2.5 mg, 5 mg)	10 mg/day
Zomig®	intranasal (**2.5 mg**, 5 mg)	10 mg/day
Combination Therapy		
sumatriptan/naproxen Treximet®	tablets (**10mg/60 mg**, 85 mg/500 mg)	170 mg/1000 mg per day

**Alternatively, patients may receive a maximum Onzetra Xsail® dose of 22 mg plus one dose of another sumatriptan product at least 2 hours later*

Pediatrics
Almotriptan, rizatriptan, **sumatriptan/naproxen, and zolmitriptan nasal spray** are the only SRAs FDA approved in children 6 to 17 years of age to treat acute migraine attacks in patients with a history of migraine with or without aura.[4, 8, 16-22] Children/ adolescents 6 to 17 years of age prescribed propranolol weighing less than 40 kg should not receive rizatriptan concurrently. Maximum recommended pediatric doses for SRAs are summarized in Table 2. Dosages exceeding these recommendations will be reviewed.

Table 2: Maximum Recommended Daily Pediatric Dosages for FDA-Approved SRAs[1-4, 8, 16, 17]		
Drug	**Patient Characteristics**	**Maximum Daily Dosage**
Monotherapy		
almotriptan	12 to 17 years of age	25 mg/day
rizatriptan	6 to 17 years of age (without propranolol) *20 to 39 kg* *40 kg or greater* 6 to 17 years of age (with propranolol*) *40 kg or greater*	 5 mg 10 mg 5 mg
zolmitriptan nasal spray	**12 to 17 years of age**	**10 mg**
Combination Therapy		
sumatriptan/naproxen	**12 to 17 years of age**	**85 mg/500 mg**

The remaining SRAs are not FDA-approved for use in patients less than 18 years of age as safety and efficacy have not been established in this patient population. Additionally, patients less than 18 years of age have demonstrated a significant placebo response following SRA use as well as an adverse event profile, including serious adverse events, comparable to that seen in adults.[5, 10, 11, 23]

No significant data are available evaluating SRA use in pediatric patients younger than 6 years of age. In limited randomized, controlled trials, sumatriptan nasal spray has demonstrated some efficacy in mitigating migraine attacks in adolescents; children as young as 6 years of age have achieved favorable responses with intranasal sumatriptan in a few small randomized and open-label studies.[24-27] However, oral sumatriptan tablets used in children 8 to 16 years of age to treat acute migraine attacks were not significantly better than placebo.[28] A few small studies with oral zolmitriptan have shown mixed outcomes.[29,30] Although not FDA-approved, Table 3 summarizes SRA doses that have been utilized in the pediatric population. **Due to lack of definitive efficacy, prescriptions for SRAs not FDA-approved for pediatric patients will be reviewed in patients 6 to 18 years of age.**

Table 3: Non FDA-Approved Pediatric Dosages for Select SRAs[24-27, 29, 30]		
Drug	**Patient Characteristics**	**Dose Utilized Per Headache**
sumatriptan intranasal spray	6 to 17 years of age	20 mg
subcutaneous	6 to 18 years of age	0.06 mg/kg
	6 to 16 years of age *< 30 kg* *> 30 kg*	 3 mg 6 mg
zolmitriptan tablets	6 to 18 years of age	2.5 mg

2. **Duration of Therapy**

Migraine headache is a chronic, recurrent condition usually requiring long-term, intermittent therapy for pain relief. Serotonin 5-HT$_{1B/1D}$ receptor agonists are approved for acute treatment of migraine attacks and may be utilized indefinitely to manage migraine headaches provided that the maximum dosage recommendation is not exceeded in a 24-hour period.[22, 31, 32] Additionally, the safety of treating more than 3 or 4 headaches during a 30-day time period has not been established. Children/ adolescents 6 to 17 years of age are allowed only one rizatriptan dose per 24 hours, as safety and efficacy have not been determined for multiple rizatriptan doses in pediatric patients.[8] Maximum quantities of serotonin 5-HT$_{1B/1D}$ receptor agonists to be dispensed in a 30-day time period, based on number of headaches to be treated, are summarized in Tables 4 and 5 for adults and adolescents, respectively. Patient profiles documenting quantities of serotonin 5-HT$_{1B/1D}$ receptor agonists that exceed these recommendations will be reviewed.

Table 4: Maximum Recommended SRA Adult Dosage Frequency[1-17]		
Drug	**Maximum Number of Headaches Treated per 30 Days**	**Recommended Prescribed Tablet Number/Sprays or Dose per 30 Days**
Monotherapy		
almotriptan tablets	4 headaches	8 x 12.5 mg tablets or 100 mg
eletriptan tablets	3 headaches	6 x 40 mg tablets or 240 mg
frovatriptan tablets	4 headaches	12 x 2.5 mg tablets or 30 mg
naratriptan tablets	4 headaches	8 x 2.5 mg tablets or 20 mg
rizatriptan tablets orally-disintegrating tablets (ODT) *propranolol patients (regular or ODT)*	 4 headaches 4 headaches 4 headaches	 12 x 10 mg tablets or 120 mg 12 x 10 mg ODT or 120 mg 12 x 5 mg tablets/ODT or 60 mg
sumatriptan intranasal spray **intranasal powder** oral tablets subcutaneous injection	 4 headaches **4 headaches** 4 headaches ----[+]	 8 x 20 mg spray or 160 mg **8 x 22 mg powder or 176 mg** 8 x 100 mg tablets or 800 mg[*] ----
zolmitriptan intranasal tablets orally-disintegrating tablets	 4 headaches 3 headaches 3 headaches	 8 sprays or 40 mg 6 x 5 mg tablets or 30 mg[*] 6 x 5 mg tablets or 30 mg[*]
Combination Therapy		
sumatriptan/naproxen tablets	5 headaches	10 tablets or 850 mg/5000 mg

[*]After May 1st, 2002, the Texas Medicaid Vendor Drug Program extended dosage limits for oral sumatriptan to not exceed 900 mg/month (9 x 100 mg tablets) and oral zolmitriptan to not exceed 40 mg/month (8 x 5 mg tablets).

*[+]Patients taking Imitrex® or **Sumavel® DosePro®** should not receive more than 2 subcutaneous injections in a 24-hour time period**; patients taking Zembrace™ should not receive more than 4 subcutaneous injections per day***

Table 5: Maximum Recommended SRA Pediatric Dosage Frequency[4, 8, 16, 17]		
Drug	**Maximum Number of Headaches Treated per 30 Days**	**Recommended Prescribed Tablet Number/Sprays or Dose per 30 Days**
Monotherapy		
almotriptan	**4 headaches**	**8 x 12.5 mg tablets or 100 mg**
rizatriptan	***patients without propranolol*** **20 to 39 kg: 4 headaches** **≥ 40 kg: 4 headaches** ***propranolol patients*** **4 headaches**	 **4 x 5 mg tablets or 20 mg** **4 x 10 mg tablets or 40 mg** **4 x 5 mg tablets or 20 mg**
zolmitriptan nasal spray	**4 headaches**	**8 x 5 mg spray or 40 mg**
Combination Therapy		
sumatriptan/naproxen	**2 headaches**	**2 tablets or 170 mg/1000 mg**

3. ***Duplicative Therapy**

Using two or more serotonin 5-HT$_{1B/1D}$ receptor agonists concurrently is not justified due to lack of additional therapeutic benefit and the potential for additive vasospastic effects. Patient profiles documenting receipt of multiple serotonin 5-HT$_{1B/1D}$ receptor agonists will be reviewed.

4. ***Drug-Drug Interactions**

Patient profiles will be reviewed to identify those drug regimens which may result in clinically significant drug-drug interactions. Clinically relevant drug-drug interactions for serotonin 5-HT$_{1B/1D}$ receptor agonists are summarized in Tables 6 and 7. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 6: Summary of Significant SRA Drug Interactions[2, 4-17, 34]							
Triptan	*Interacting Drugs*						
	Amphetamines	CYP3A4 inhibitors	Ergots	Linezolid	MAOIs^{+}	Propranolol	SNRIs$^{\#}$/SSRIs*
almotriptan	√	√	√	√	√	----	√
eletriptan	√	√	√	√	√	----	√
frovatriptan	√	----	√	√	√	ns	√
naratriptan	√	----	√	√	√	----	√
rizatriptan	√	----	√	√	√	√	√
sumatriptan	√	----	√	√	√	----	√
zolmitriptan	√	----	√	√	√	ns	√

ns = not significant
$^{+}$MAOIs = monoamine oxidase inhibitors; $^{\#}$SNRIs = serotonin-norepinephrine reuptake inhibitors; *SSRIs = selective serotonin reuptake inhibitors

Table 7: SRA Drug-Drug Interactions[2, 4-17, 34]

Target Drug^	Interacting Drug	Interaction	Recommendations	Clinical Significance~
SRAs	amphetamines	concurrent administration may stimulate serotonin neurotransmission and increase risk of serotonin syndrome (e.g., mental status changes, diaphoresis, tremor, fever), as amphetamines increase serotonin release	avoid combination, if possible; if adjunctive therapy necessary, observe for signs/symptoms of serotonin syndrome and adjust therapy as indicated	1-severe (CP)
almotriptan, eletriptan	CYP3A4 inhibitors (e.g., azole antifungals, macrolides)	adjunctive administration of CYP3A4 inhibitors with almotriptan or eletriptan (CYP3A4 substrates) may result in increased almotriptan/eletriptan serum levels and enhanced pharmacologic/toxic effects, including potential for vasospastic and/or cardiac events	eletriptan contraindicated for use within 72 hours of strong CYP3A4 inhibitor; lower almotriptan dosages required when used concurrently with CYP3A4 inhibitors (maximum dose, 12.5 mg); an alternative antifungal that does not inhibit CYP3A4 (e.g., terbinafine) may be an alternative for azoles	**contraindicated**, moderate (DrugReax) **1-severe**, 2-major (CP)
SRAs	ergot derivatives/ ergot-type medications (e.g., bromocriptine)	combined administration may result in additive vasospastic effects	SRAs should not be used within 24 hours of ergot derivatives/ergot-type medications	contraindicated (DrugReax) 1-severe (CP)
SRAs	linezolid	concurrent administration with SRAs metabolized by monoamine oxidase (MAO) may increase serotonin levels and the potential for serotonin syndrome, as linezolid is nonselective monoamine oxidase inhibitor (MAOI)	adjunctive administration or administration within 14 days of MAOI discontinuation is contraindicated by SRA manufacturers; if combination necessary, observe patient closely for signs/symptoms of serotonin syndrome; eletriptan is not metabolized by MAO, and frovatriptan, naratriptan do not inhibit MAO - may be safe alternatives; almotriptan is metabolized by MAO but does not require dosage adjustments when used with MAOIs - may also be alternative	contraindicated (DrugReax) 2-major (CP)

Table 7: SRA Drug-Drug Interactions (continued)[2, 4-17, 34]				
Target Drug^	**Interacting Drug**	**Interaction**	**Recommendations**	**Clinical Significance~**
SRAs	MAOIs+, including selegiline (high doses)	adjunctive administration of SRAs with other medications having serotonergic properties like MAOIs, which decrease serotonin metabolism, may increase serotonin levels and the potential for serotonin syndrome; selegiline in doses greater than 10 mg daily may behave like an MAOI	adjunctive administration or administration within 14 days of MAOI discontinuation is contraindicated by SRA manufacturers; if combination necessary, observe patient closely for signs/symptoms of serotonin syndrome; eletriptan is not metabolized by MAO, and frovatriptan, naratriptan do not inhibit MAO - may be safe alternatives; almotriptan is metabolized by MAO but does not require dosage adjustments when used with MAOIs and may also be alternative	contraindicated (DrugReax) 1-severe, 2-major (CP)
rizatriptan	propranolol	adjunctive rizatriptan-propranolol administration increases the rizatriptan AUC by as much as 70% as propranolol inhibits rizatriptan metabolism	reduce rizatriptan doses (maximum daily dose, 15 mg); observe patients for enhanced rizatriptan pharmacologic/adverse effects when co-administered	moderate (DrugReax) 2-major (CP)
SRAs	SNRIs*/SSRIs#	adjunctive administration of SRAs with other medications having serotonergic properties like SNRIs/SSRIs may increase serotonin levels and the potential for serotonin syndrome	avoid combination, if possible; if combined therapy necessary, monitor patient closely for signs/symptoms of serotonin syndrome and modify drug therapy as necessary	major (DrugReax) 2-major (CP)

*~CP = Clinical Pharmacology; #SNRIs = serotonin-norepinephrine reuptake inhibitors; *SSRIs = selective serotonin reuptake inhibitors; ^SRAs = serotonin 5-HT$_{1B/1D}$ receptor agonists*

REFERENCES

1. DRUGDEX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com.libproxy.uthscsa.edu. **Accessed December 4th, 2016.**
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc; **2016**. Available at: http://www.clinicalpharmacology.com. **Accessed December 4th, 2016.**
3. Drug Facts and Comparisons. Clin-eguide [database online]. St. Louis, MO: Wolters Kluwer Health, Inc; 2014. Available at: http://clineguide.ovid.com.ezproxy.lib.utexas.edu. Accessed December 8th, 2014.
4. Almotriptan (Axert®) Package Insert. Janssen Pharmaceuticals, Inc., August 2014.
5. Eletriptan (Relpax®) Package Insert. Pfizer, Inc., November 2013.
6. Frovatriptan (Frova®) Package Insert. Endo Pharmaceuticals, Inc., October 2013.
7. Naratriptan (Amerge®) Package Insert. GlaxoSmithKline, **August 2015.**
8. Rizatriptan (Maxalt® and Maxalt-MLT®) Package Insert. Merck & Co, Inc., **March 2015.**
9. Sumatriptan tablets (Imitrex®) Package Insert. GlaxoSmithKline, November 2013.
10. Sumatriptan injection (Imitrex®) Package Insert. GlaxoSmithKline, **October 2015.**
11. Sumatriptan nasal spray (Imitrex®) Package Insert. GlaxoSmithKline, November 2013.
12. **Sumatriptan nasal powder (Onzetra Xsail®) Package Insert. Avanir Pharmaceuticals, Inc., January 2016.**
13. **Sumatriptan injection (Sumavel® DosePro®) Package Insert. Endo Pharmaceuticals Inc., June 2016.**
14. **Sumatriptan succinate injection (Zembrace™ SymTouch™) Package Insert. Promius Pharma, LLC, January 2016.**
15. Zolmitriptan tablets and orally disintegrating tablets (Zomig® and Zomig-ZMT®) Package Insert. Impax Pharmaceuticals, **November 2016.**
16. Zolmitriptan nasal spray (Zomig®) Package Insert. Impax Pharmaceuticals, **November 2016.**
17. Sumatriptan/naproxen tablets (Treximet®) Package Insert. Pernix Therapeutics, **May 2016.**
18. Lewis DW, Winner P, Hershey AD, Wasiewski WW, for the Adolescent Migraine Steering Committee. Efficacy of zolmitriptan nasal spray in adolescent migraine. Pediatrics. 2007;120:390-6.
19. **Winner P, Farkas V, Stillova H, et al. Treatment of acute migraine in adolescents: results of a randomized, double-blind, multi-center, parallel-group study (TEENZ). Headache. 2016;56:1107-19.**
20. Ahonen K, Hamalainen ML, Eerola M, Hoppu K. A randomized trial of rizatriptan in migraine attacks in children. Neurology. 2006;67:1135-40.
21. Winner P, Lewis D, Visser WH, et al, for the Rizatriptan Adolescent Study Group. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double-blind, placebo-controlled study. Headache. 2002;42:49-55.
22. Visser WH, Winner P, Strohmaier K, et al. Rizatriptan Protocol 059 and 061 Study Groups. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: results from a double-blind, single-attack study and two open-label, multiple-attack studies. Headache. 2004;44:891-9.
23. Winner P, Linder SL, Lipton RB, et al. Eletriptan for the acute treatment of migraine in adolescents: results of a double-blind, placebo-controlled trial. Headache. 2007;47(4):511-8.
24. Ahonen K, Hamalainen ML, Rantala H, Hoppu K. Nasal sumatriptan is effective in treatment of migraine attacks in children: a randomized trial. Neurology. 2004;62:883-7.
25. Winner P, Rothner AD, Saper J, et al. A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. Pediatrics. 2000;106:989-97.
26. Ueberall MA, Wenzel D. Intranasal sumatriptan for the acute treatment of migraine in children. Neurology. 1999;52:507-10.
27. Winner P, Rothner AD, Wooten JD, et al. Sumatriptan nasal spray in adolescent migraineurs: a randomized, double-blind, placebo-controlled, acute study. Headache. 2006;46:212-22.

28. Hamalainen ML, Hoppu K, Santavuori P. Sumatriptan for migraine attacks in children: a randomized placebo-controlled study. Do children with migraine respond to oral sumatriptan differently from adults? Neurology. 1997;48(4):1100-3.
29. Evers S, Rahmann A, Kraemer C, et al. Treatment of childhood migraine attacks with oral zolmitriptan and ibuprofen. Neurology. 2006;67:497-9.
30. Rothner AD, Wasiewski W, Winner P, et al. Zolmitriptan oral tablet in migraine treatment: high placebo responses in adolescents. Headache. 2006;46:101-9.
31. Lewis D, Ashwal S, Hershey A, et al. Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents. Report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004;63:2215-24.
32. **Silberstein, SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology® 2012;78:1337-45.**
33. Loder E. Triptan therapy in migraine. N Engl J Med. 2010;363:63-70.
34. DRUG-REAX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com.libproxy.uthscsa.edu. **Accessed December 7th, 2016.**

Prepared by

- Drug Information Service, the University of Texas Health Science Center at San Antonio.
- The College of Pharmacy, the University of Texas at Austin.